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## The therapeutic potential of poly(ADP-ribose) polymerase inhibitors.

Virag L, Szabo C.

Inotek Pharmaceutical Corp., Beverly, Massachusetts 01915, USA.

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Poly(ADP-ribose) polymerase-1 (PARP-1) is a member of the PARP enzyme family consisting of PARP-1 and several recently identified novel poly(ADP-ribosylating) enzymes. PARP-1 is an abundant nuclear protein functioning as a DNA nick-sensor enzyme. Upon binding to DNA breaks, activated PARP cleaves NAD(+) into nicotinamide and ADP-ribose and polymerizes the latter onto nuclear acceptor proteins including histones, transcription factors, and PARP itself. Poly(ADP-ribosylation) contributes to DNA repair and to the maintenance of genomic stability. On the other hand, oxidative stress-induced overactivation of PARP consumes NAD(+) and consequently ATP, culminating in cell dysfunction or necrosis. This cellular suicide mechanism has been implicated in the pathomechanism of stroke, myocardial ischemia, diabetes, diabetes-associated cardiovascular dysfunction, shock, traumatic central nervous system injury, arthritis, colitis, allergic encephalomyelitis, and various other forms of inflammation. PARP has also been shown to associate with and regulate the function of several transcription factors. Of special interest is the enhancement by PARP of nuclear factor kappa B-mediated transcription, which plays a central role in the expression of inflammatory cytokines, chemokines, adhesion molecules, and inflammatory mediators. Herein we review the double-edged sword roles of PARP in DNA damage signaling and cell death and summarize the underlying mechanisms of the anti-inflammatory effects of PARP inhibitors. Moreover, we discuss the potential use of PARP inhibitors as anticancer agents, radiosensitizers, and antiviral agents.

### Publication Types:

- Review
- Review, Academic

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1: Curr Pharm Biotechnol 2002 Sep;3(3):275-83

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## Modulating poly (ADP-ribose) polymerase activity: potential for the prevention and therapy of pathogenic situations involving DNA damage and oxidative stress.

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Poly (ADP-ribose) polymerase is a zinc-finger DNA-binding enzyme which detects and signals DNA strand breaks generated either directly during base excision repair, or indirectly by genotoxic agents such as oxygen radicals. In response to genotoxic injury, PARP catalyses the synthesis of poly (ADP-ribose), from its substrate beta-NAD<sup>+</sup> and this polymer is covalently attached to several nuclear proteins and PARP itself. As a result, PARP converts DNA breaks into intracellular signals which activate DNA repair programs or cell death options. Several studies have also shown that PARP is involved in either necrosis and subsequent inflammation or apoptosis. Although this enzyme is not indispensable during the latter cell death program, it has been demonstrated that PARP plays a facilitating role in this process. PARP is activated at an intermediate stage of apoptosis and is then cleaved and inactivated at a late stage by apoptotic proteases, namely caspase-3/CPP-32/Yama/apopain and caspase-7. This cleavage prevents necrosis during apoptosis, avoiding inflammation. All these functions, and the observation that PARP is an abundant and highly conserved enzyme, suggest that this enzyme plays a pivotal role, particularly in the maintenance of genomic DNA stability, apoptosis and in the response to oxidative stress. Since these situations are found in cancer, inflammation, autoimmunity (such as diabetes), myocardial dysfunction, certain infections, ageing and radiation/chemical exposure, attempts have been made to modulate PARP activity. With regard to the increasing interest towards PARP, the aim of this review is to explain the cellular role of PARP and the advantages of modulating its activity in diverse preventive or therapeutic strategies.

### Publication Types:

- Review
- Review, Tutorial

**Mutation Research/DNA Repair**

Volume 460, Issue 1 , 30 June 2000, Pages 1-15

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**Poly(ADP-ribose) polymerase-1: what have we learned from the deficient mouse model?**

Sydney Shall<sup>1</sup>, and Gilbert de Murcia

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**Abstract**

Poly (ADP-ribose) polymerase (113 kDa; PARP-1) is a constitutive factor of the DNA damage surveillance network developed by the eukaryotic cell to cope with the numerous environmental and endogenous genotoxic agents. This enzyme recognizes and is activated by DNA strand breaks. This original property plays an essential role in the protection and processing of the DNA ends as they arise in DNA damage that triggers the base excision repair (BER) pathway. The generation, by homologous recombination, of three independent deficient mouse models have confirmed the caretaker function of PARP-1 in mammalian cells under genotoxic stress. Unexpectedly, the knockout strategy has revealed the instrumental role of PARP-1 in cell death after ischemia-reperfusion injury and in various inflammation process. Moreover, the residual PARP activity found in PARP-1 deficient cells has been recently attributed to a novel DNA damage-dependent poly ADP-ribose polymerase (62 kDa; PARP-2), another member of the expanding PARP family that, on the whole, appears to be involved in the genome protection. The present review summarizes the recent data obtained with the three PARP knockout mice in comparison with the chemical inhibitor approach.

**Author Keywords:** Cellular response to DNA damage; Genomic instability; Base excision repair; Type I Diabetes; NF- $\kappa$ B; NAD<sup>+</sup> metabolism

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